Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Drugs for Thyrotoxicosis

SIR,—The letter from Mr. Geoffrey Chamberlain (April 20, p. 1087) once again expresses the dogmatism of some obstetricians and many surgeons who continue to advocate routine partial thyroidectomy for the treatment of thyrotoxicosis during pregnancy. We would be the first to confess that this is not infrequently desirable, particularly if the opportunity is taken to operate upon a pregnant thyrotoxic woman and so avoid the inconvenience of hospital admission later on when she has an infant. Nevertheless, the hyperdynamic state of pregnancy may well produce many of the symptoms and signs of thyrotoxicosis, and if these are encountered in association with a goitre diagnostic criteria for toxicity may be too readily established. There are difficulties inherent in many of the diagnostic tests during pregnancy which it may not in any case be practicable to employ. In a study of thyroid function during pregnancy we have found in Aberdeen an incidence of nearly 70% of goitre in a group of 184 pregnant women, the comparable incidence in a control group of 116 presumably non-pregnant hospital and factory workers being 35%. This appearance of goitre is secondary to high iodine requirements, and the apparently high incidence of pregnancy goitre is certainly not peculiar to Aberdeen. The possibility of diagnostic doubt during pregnancy makes it important not to carry out irreversible procedures on patients first developing apparent toxicity during pregnancy, and our experience is that pregnancy is more likely to promote remission of, rather than exacerbation of, pre-existing thyrotoxicosis.

Accordingly it is preferable to manage patients throughout pregnancy with drug treatment, as we have previously advocated in your columns,[1] always ensuring that the mother is never over-treated, as only in such circumstances does foetal thyroid enlargement develop with possible hypothyroidism. There should be no hesitation in recommending operation if difficulties arise regarding medical management, but this is rare.

It is a somewhat devious argument to maintain that because there are features common to pregnancy and hyperthyroidism, and because the pregnant woman tolerates high hormone levels well, therefore drugs but not surgery are contraindicated.

We would respectfully submit that it is no argument, scientific or logical, to adduce the alleged views of obstetricians "on both sides of the Atlantic" regarding the primary treatment of a medical condition, and I doubt whether we as physicians would be prepared to give an opinion on the management of delayed labour.—We are, etc.,

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REFERENCE

[1] Crooks, J., Khair, S. A., Macgregor, A. G., and Turnbull, A. C., *Brit. med. J.*, 1962, **2**, 1259.

SIR,—In "Drugs for Thyrotoxicosis" (To-day's Drugs, March 30, p. 863) you fail to mention phenobarbitone in the control of thyrotoxicosis. Although this drug may not affect the mechanism of hormone production, it does much to control the symptoms of thyrotoxicosis, especially in the early stages of treatment, when antithyroid drugs are still relatively ineffective.

Moreover, the amelioration of symptoms in these stages is important in establishing the patient's confidence in the effectiveness of the treatment, which he might otherwise discontinue.—I am, etc.,

Nicosia, Cyprus. S. H. NICOLAIDES.

Oral Contraception and Coagulability

SIR,—Dr. Armand J. Quick (March 16, p. 744) implies that our results are unreliable and may be misleading. The variations pointed out by Dr. Quick between individuals and from one laboratory to another using different techniques is no relevant argument against the reliability of our observations. The coagulation activities measured when the patient is on drug therapy should necessarily be compared with the values in the same person before and after therapy.

The recorded uniform increase in the antihaemophilic A factor (VIII) activity of up to two or three times the pre-treatment level is highly significant. The reversal to the pre-treatment levels of both factor VIII and the cephalin time after discontinuation provides further evidence.

Dr. Quick's comparison of increases in clotting factors with the increase in platelets in cases of thrombocythaemia associated with a bleeding tendency is also misplaced because in the latter situation the platelets are abnormal.

The possible risk of thrombosis during this type of hormonal therapy has to be considered very seriously. The problem is complex and was not specifically discussed in our paper. We only stated the changes observed. Quick obviously does not believe that an increase of two to three times the factor VIII activity has any relation to a predisposition to thrombosis. We may hope that this is so, but the possibility cannot be dismissed by arguing, as Dr. Quick does, that normal people already have about 20 times more of this factor than needed.

In clinical conditions which are notorious for an increased tendency to thrombosis, such as in the post-operative state,[1] in cases of intravascular haemolysis,[2] and in some other conditions, we have observed a similar marked increase in factor VIII activity. This points to a relationship.

The case reports of thrombotic disease associated with the use of oral contraceptives do, of course, not prove any definite causal relationship. As Dr. Quick, however, has raised the question I would like to draw attention also to a recent study from Chicago[3] on the use of oestrogens in men surviving acute myocardial infarction. Among 60 men who started on high dosage of oestrogens there were four (6.7%) non-fatal and nine (15%) fatal events, or a total of 13 (21.7%) recurrent myocardial infarctions, in the first two months of drug therapy. The corresponding incidence for the placebo group of 64 patients was a total of four (5.9%) myocardial infarctions, and in 96 men on a low dosage the total incidence was four (4.2%). Realizing that thrombosis plays an important role as the precipitating factor in coronary occlusion, the enormous increase in infarctions and mortality on hormonal therapy is alarming.

Dr. Quick recommended the study of "the more likely target, the vessel wall," and refers to his theory

"that venous thrombosis is initiated by an injury of the vessel wall which causes a localized liberation of tissue thromboplastin to produce a clot attached to the area of injury."[4] There is more evidence against than in favour of this theory. Tissue thromboplastin is an intracellular particulate substance, and cellular destruction, therefore, is necessary to release it. Further, the difference between thrombosis and intravascular coagulation has by now been well established. If Dr. Quick's theory was correct one would not expect venous thrombosis in factor VII deficiency cases. We have, however, observed post-operative thrombo-embolism in two patients with total factor VII deficiency.[5]

Platelets play a major role in the first stages of thrombus formation. Since the discovery of adenosine diphosphate[6] as a key-factor at this stage and the significance of the platelet surface clotting systems for the progression and consolidation of the platelet thrombus it seems more profitable to pursue this line of investigation along with studies on plasma coagulation. —I am, etc.,

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Goitre in Klinefelter's Syndrome

SIR,—A nodular goitre is reported as an incidental finding at post-mortem of a 71-year-old male with chromatin-positive Klinefelter's syndrome (March 30, p. 866). That this is not in fact a mere coincidence is suggested by many similar reports in the literature, summarized by Burt *et al.*[1] No information is available whether these individuals fall into the chromatin-negative group of Klinefelter's syndrome or whether they have a female sex chromatin pattern and an XXY chromosomal constitution. Recently Davis *et al.*[2] reported that three of four XXY individuals studied had an abnormally low radio-iodine uptake. An editorial[3] in the same issue refers to the importance of the differential incidence of common diseases in individuals of abnormal chromosomal constitution and the light that this might throw on aetiological factors. In a recent study,[4] one of 12 infertile males with non-toxic nodular goitre, treated surgically, was shown to be of XXY chromosomal constitution. On the other hand none of 23 males with primary thyrotoxicosis whose sex chromatin was studied showed a female pattern.

It would seem likely, therefore, that at least non-toxic nodular goitre, a disease more characteristically present in females, is more frequent in XXY individuals than in normal males.—I am, etc.,

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Antibiotic Growth Stimulation

SIR,—In response to the consideration of my work in your annotation on "Antibiotics as Human Food Supplements" (December 15, 1962, p. 1594) and the letter on "Antibiotic Growth Stimulation" (Dr. M. Lev, February 23, 1963, p. 539) I suggest that evidence for direct modes of action does not exclude stimulation by antibacterial action and vice versa. The direct and indirect effects may be synergistic and are certainly not mutually exclusive. An action established for micro-organisms in the intestinal tract does not necessarily delineate the effect upon the mucosal cells which are a part of a more highly organized system, and the establishment of an action upon the host cells does not necessarily preclude a different action upon the microbial cells.

In 1946 Peter Moore, E. B. Hart, C. A. Elvehjem, and I discovered the phenomenon of antibiotic growth stimulation.[1] By typical interdepartmental co-operation with the Department of Bacteriology of the University of Wisconsin we were able to present evidence for the antibacterial action. We discussed this and noted: "The possibility that these agents are acting systemically cannot be overlooked."

Several years later the discovery of commercial potential in the effect[2] led many investigators to the question of the mode of action. We[3] began germ-free animal experiments with antibiotics on December 1, 1950. Streptomycin showed no clear effect. The first experiment with terramycin at 25 mg./kg., showed a positive response in germ-free chicks ($P<0.001$). Knowing that a wide range of levels was effective in classic (conventional) chicks, we doubled the quantity of antibiotics in subsequent experiments. The results were negative. The next month a series of experiments was begun with low levels of antibiotics. The results were positive. The data,[3] showed that the "high" level of antibiotics gave no stimulation while the "low" level stimulated growth ($P<0.001$) in germ-free chicks. No definitive experiment has been reported in the decade since our germ-free work. While several groups have verified our results[4-6] with high levels, none seem able to break the "barrier" to try 10–15 mg. antibiotic per kg. diet.

Stress is an important factor in the interpretation of the results. On some farms antibiotics have no effect; on others, a dramatic effect is shown. Unless the proper experimental conditions are provided for the effect, a thousand negative results carry little weight.

The evidence for a direct action is summarized.[7] Results with germ-free chicks and poults fed low levels of antibiotics were verified by Nickell,[8] who showed the stimulation of germ-free plants by antibiotics. Growth stimulation is found in conventional chicks with non-bactericidal compounds—that is, arsenicals, detergents, inactivated antibiotics, and a variety of dyes. Many micro-organisms have been shown to be stimulated by sub-inhibitory doses of antimicrobial agents.

Further evidence is the fact that the growth stimulation of antibiotics is only one part of the total picture. The broad view is given in a concept termed *hormoligosis*[7] (from the Greek *hormo*, meaning to excite, and *oligo*, meaning small quantities). The generalized hypothesis states that any inhibitory agent, when administered in quantities substantially lower than the minimum inhibitory quantity, can be stimulatory to the organism. In recent studies on the action of antibiotics